Mini Review

Journal Of Clinical & Medical Images Case Reports

*Open Access, Volume - 1*

# Molecular-Genetic Features In The Diagnosis Of Odontogenic Tumors

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**Received Date** : Oct 19, 2021
**Accepted Date** : Nov 05, 2021
**Published Date** : Nov 08, 2021
**Archived** : www.jcmimagescasereports.org


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## Abstract

Benign odontogenic formations cause one and the same controversial situation known to pathologists for the last century. Some researchers believe that they are indeed benign. These formations are often asymptomatic, and the X-ray picture is not always reliable. There are currently no clear criteria for predicting the development of relapse. Based on modern molecular morphological techniques, it is important to identify the molecular mechanisms of recurrence, formation and growth of ameloblastoma and develop appropriate treatment methods. This review summarizes the background, current status, and future perspectives of odontogentic tumor in the multimodal treatment. The further trials to investigate the clinical benefits of diagnosis and treatment of odontogenic tumor were needed.
**Keywords:** genetics, ameloblastoma, SEER, GNAS, BRAFV600E

## Introduction

In recent years, the total number of detected benign odontogenic tumors has increased significantly. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, they account for only 0.2% of all tumor sites. In 2018, 3450 new cases of primary neoplastic diseases of the bones were registered, which is rather small compared with the 1,700,000 new cases of oncological diseases reported in general [1].

### Diagnosis and clasification of Odontogenic Tumor

According to the latest histological classification of odontogenic tumors of the head and neck by WHO, published in 2005, the term “keratocystic odontogenic tumor” was introduced to describe parakeratosis variants of “keratocysts” due to their unique histopathology and dual nature, showing clinical and pathological features of cysts and benign tumors. According to Kotelnikov et al., the most frequent cases of bone formations are in benign tumors and tumor-like lesions of bones, but the diagnostic sensitivity is low due to their long asymptomatic course and difficulties in making a differential diagnosis [2, 3]. Some authors hold that the true benign tumors and tumor-like bone lesions are not fully understood [4]. Benign tumors and tumor-like lesions include such nosological forms as bone cysts, fibrous dysplasia, nonossifying fibroma, and Paget's disease. The localization and age-related variations in the above odontogenic pathology differ and are an important diagnostic criterion [2, 5]. A large group of benign bone formations is made up of tumors of odontogenic origin, and among tumor-like lesions - fibro-bone dysplasia of the maxillofacial region. Benign neoplasms and precancerous formations of the bones of the MFOmainly affect people 10 to 20 years old and are accompanied by the formation of significant deformities and asymmetries of the face [6]. Therefore, the gold standard for the diagnosis of the presented nosologies is a set of data obtained via clinical, radiation, and pathomorphological approaches. However, this combination of methods is no longer sufficient in actual practice.

### Clinical feature of Odontogenic Tumor

Since the tumor may be prone to local aggressive growth, require radical surgical intervention, take into account the risk of recurrence, whether this formation of inflammatory diseases wears a "mask". Differentiation using pathomorphological and diagnostic methods can be difficult and insufficient due to the combination of nonspecific histological and radiological pictures. For example, there are difficulties in differentiating between fibrous dysplasia and ossifying fibroma due to the fact that fibrous dysplasia does not have clear radiological semiotics and may tend to show ossifying fibroids [10]. In such cases, the amount of surgery and subsequent therapy required will depend on the diagnosis. If the diagnosis and prognostic course of the disease are inaccurately presented, patients may need reoperation in

**Citation:** Nigina Abdukhalik-Zade; Jasur Rizaev, Abduavaz Ganiev; Lalita Yunusova; Sobirjon Mamarajabov; Kamron Olimjonov. Molecular-Genetic Features In The Diagnosis Of Odontogenic Tumors. J Clin Med Img Case Rep. 2021; 1(1): 1012.

case of recurrence or malignancy of the tumor. Of note, the probability of malignancy with fibrous dysplasia is less than 1%, but malignant fibrous dysplasia can transform into an aggressive tumor, such as osteosarcoma (about 70% of cases), fibrosarcoma (about 20% of cases), chondrosarcoma (about 10% of cases), or malignant fibrous histiocytoma (about 4%) [11].To differentiate fibrous dysplasia from other fibrous-bone lesions, a genetic test is used to determine the mutation in the GNAS gene. This mutation has been identified and confirmed in various samples of patients with fibrous dysplasia using Sanger sequencing. It has been proven that a mutation in this gene is linked to the molecular pathogenesis of fibrous dysplasia, being specific for it and not occurring in other fibrous-bone lesions [12–14].

**Molecular mechanism of Odontogenic Tumor**

The molecular mechanism underlying the emergence of benign neoplasms and precancerous lesions of the bones of the PMO continues to be actively studied, and the search for candidate genes responsible for the onset of the disease, which can also serve as markers of this group of nosologies, is ongoing. The study of the above diseases from a genetic perspective has become more relevant due to the active development of molecular genetic technologies, including next-generation sequencing (NGS) technology. The value and application of NGS in practical MLC to clarify the etiology of a disease and improve the quality of medical care for patients is not yet routine practice. Data supporting an individual approach to the management of a particular patient are lacking at present, so the search for new genetic markers and their place in the clinical, histological, and radiological picture is an extremely important task for applied medicine. The study of candidate genes significant for the development of these diseases is a step towards achieving targeted therapy for tumors and tumor-like diseases. The WHO published a classification (2013) of tumors of the maxillofacial region (WHO Classification of Tumors of Soft Tissue and Bone), according to which tumors of the maxillofacial bones are divided into 58 types. In this classification, in addition to the classical division of tumors into malignant and benign, intermediate tumors characterized by locally destructive growth, such as desmoplastic fibroma, are also distinguished. Also mentioned are tumors of an undetermined neoplastic nature (tumor-like diseases), a group that includes solitary bone cyst, fibrous dysplasia, osteofibrous dysplasia, and chondromesenchymal hamartoma [4]. It should be emphasized that this classification mentions no such tumor subtype as "cementoma", which CIS countries continues to distinguish as a separate group; these lesions are classified into the following types: benign cemento-blastoma, cementing fibroma, periapical cementing dysplasia, and gigantoform cementoma [16]. In 2017, the WHO published a new classification of "head and neck tumors" (WHO Classification of Head and Neck Tumors), which characterizes in detail odontogenic tumors and cysts of the CLE. It does not separately emphasize osteofibrous dysplasia, which is often found only in long tubular bones, but ossifying fibroma is clearly highlighted. Furthermore, in this classification, cement-ossifying dysplasia is now considered a special case of ossifying fibroma [17]. The molecular genetic features of ameloblastomas of different types (peripheral, monocystic, metastatic), as well as squamous cell odontogenic tumor, calcifying epithelial odontogenic tumor, and adenomatoid odontogenic tumor, are described.

**Clinical feature and diagnosis, and melecular mechanism of Ameoblastomas**

According to the 2005 WHO classification, ameloblastoma belongs to the group of benign odontogenic tumors [Olimid D.A. et al., 2014]. Ameoblastomas make up 10% of all odontogenic tumors [19], and the overwhelming majority of ameloblastomas (up to 80%) are found in the lower jaw, with a small portion arising in the upper jaw, is especially considered from the molecular genetic aspect [20]. Nagi et al. reported that ameloblastoma is observed in 1% of all cases of odontogenic tumors of the oral cavity and in 18% of all odontogenic tumors, and according to the observations of Faras et al., they account for 30.28% of all odontogenic tumor formations. Ameloblastoma is an infrequent odontogenic formation that occurs in the jaw and is susceptible to local invasion. Patients often show deformation of the jaws of the type of swelling. While the vast majority of ameloblastomas are slow-growing formations without metastatic spread, there have unfortunately been cases in which ameloblastic formations metastasized despite a benign histological landscape. The current treatments of ameloblastoma involve both conservative approaches and resection. The first-line treatment option is associated with a high risk of relapse, and the next line leads to significant deformity of the face, requiring a number of reconstructive and restorative operations to restore the functional parameters of the dentition and facial aesthetics [21]. Until 2014, the pathogenesis of ameloblastoma from a molecular perspective was largely unknown; however, a growing number of publications indicate that the activation of the mitogen-activated protein kinase (MAPK) pathway plays a significant role in the pathogenesis of ameoblastoma. With the help of polymerase chain reaction (PCR), followed by confirmatory Sanger sequencing in tissues from paraffin blocks obtained from patients with ameloblastoma, the BRAFV600E mutation was first identified [22-24]. The BRAFV600E mutation correlates with the sensitivity of cells to proteasome inhibitors. In some sources, the incidence of this mutation in ameoblastomas was 82% among analyzed cases [25]. BRAF is a serine-threonine kinase of the MAPK pathway. The V600E mutation has been found in various formations, such as melanoma, hairy cell leukemia, papillary thyroid cancer, Langerhans cell histiocytosis, and colorectal cancer [26–30]. Neoplastic transformation occurs due to the V600E mutation, which leads to the activation of the BRAF protein and downstream signaling of MEK and ERK and in turn enhances cell proliferation [31]. In addition to mutations in the BRAF gene, mutations in other genes of the MAPK pathway are also presented in the literature. Indeed, mutations have been found in the RAS gene family in 20% of ameloblastomas, including mutations in the KRAS, NRAS, and HRAS

genes [22]. The MAPK pathway is directly triggered through the activation of the type 2 fibroblast growth factor receptor (FGFR2). FGFR2 mutations are present in 6%–18% of ameloblastomas, namely in the transmembrane (C382R and V395D) or kinase domain (N549K) of the receptor. Coupling mutations in the FGFR2, RAS, and BRAF genes are present in 78%–88% of ameloblastomas [24]. In addition to mutations in the genes of the MAPK pathway, several more mutations in genes not attracted to it have been identified, including SMO, CTNNB1, PIK3CA, and SMARCB1. Of these genes, most mutations were found in SMO, being detected in 16%–39% of cases [23, 24]. Smoothened protein (SMO) is a non-classical transmembrane G-protein coupled receptor that mediates signaling in the Hedgehog pathway. The activity of the SMO protein is often inhibited by another transmembrane protein, Ptch, encoded by the PTCH1 gene that is a cellular receptor for Hh ligands. When Hh binds to Ptch, the block from the SMO protein is cleared, resulting in the activation of a group of Gli transcription factors, which in turn activate target genes by direct interaction with specific regions in the promoter region. The activation of target genes dictates a number of cellular reactions, namely the activation of proliferation and anti-apoptotic signals [32, 33]. It has been shown that polymorphisms and pathogenic variants in the germ line in the PTCH1 gene exceed the risk of developing ameloblastoma [34, 35]. Whether mutations in the MAPK and Hedgehog pathways represent two different molecular subclasses of ameloblastoma or mutations in the SMO gene are secondary changes after activation of the MAPK pathway, which is the main driver of pathogenesis, has not been proven. Apart from the three cases described, mutations in the BRAF and SMO genes are the most common among the studies conducted, and mutations in these genes are mutually exclusive. However, in 37% of cases, a joint mutation occurs in the SMO and RAS genes, and in 32% of cases, a joint mutation occurs with FGFR2 [23, 24].

## Conclusion

The results of the review obtained during the patent search of the present study indicate that recurrence of ameloblastomas in patients is not related to age or gender. The dependence of the formation of relapse in patients with ameloblastoma with the features of surgical treatment and the morphological type of tumor was revealed. These sources confirm the significant role of BRAF gene mutations in patients with ameloblastoma.

## Acknowledgments

This study was supported in part by the nonprofit organization Epidemiological and Clinical Research Information Network (ECRIN).

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